Methods: Atherectomy probes from 17 patients with coronary ISR (n=10; time post stenting 5±3 months) and with peripheral ISR (n=7; 7±3 months) versus those from 10 patients with primary lesions were immunohistochemically examined for the presence of the determinants CD34, AC133, S100, GFAP, NSE, NGFR and α-smooth muscle (SM) actin followed by computer-assisted morphometry.
Results: ISR probes demonstrated pronounced hypercellularity (942±318 cells/mm^2) compared to primary lesions (347±120 cells/mm^2, P<0.001). α-SM actin positive cells occupied 67% of intimal cells in ISR. Expression of endothelial progenitor cells (EPCs; CD34: 7.1±2.5% positive/total cells vs. 0.6±0.7%, P<0.001; AC133: 7.0±3.4% vs. 1.0±0.7%, P<0.001), dendritic cells (DCs; S100: 9.8±5.6% vs. 1.4±1.1%, P<0.001) and neural-crest derived cells (NCCs; GFAP: 7.9±2.4% vs. 3.1±1.0%; NSE: 4.4±2.6% vs. 1.3±1.6%; NGFR: 4.2±2.5% vs. 1.1±0.7%; each P<0.001) was significantly increased in ISR compared to primary lesions. Importantly, double immunostaining did not demonstrate α-SM actin positive cells exhibiting markers of EPCs, DCs or NCCs. With respect to EPC immunolabelling, AC133 could be detected in a subset of CD34 positive cells, whereas all cells stained by AC133 also expressed the CD34 antigen. Quantitatively, both EPC marker proteins revealed a significant correlation (r=0.57, P<0.01). Consistently, there were a only few cells found in ISR atherectomy probes that demonstrated coexpression of EPC, DC or NCC markers. Our data show residual 5-15% yet unidentified neointimal cells, that were not stained by any specific cell type marker used.
Conclusions: Bone-marrow and neural-crest derived cells, the most dendritic cells, are consistently found in ISR, whereas α-SM actin positive cells constitute the largest intimal cell pool. These data clearly indicate the presence of primarily extravascular cells in human ISR.

1121-48 Preprocedural Plasma Levels of C-Reactive Protein and Interleukin-6 Do Not Predict Late Coronary Angiographic Restenosis After Elective Stenting

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Aims Inflammatory markers may serve as an important prognostic predictor in patients with coronary heart diseases. In patients undergoing coronary interventions, it has been shown that baseline C-reactive protein (CRP) could predict late adverse cardiac events (clinical restenosis). However, only a few small studies have examined the relation with angiographic restenosis. In a large number of patients, we examined whether baseline plasma levels of CRP and IL-6 may predict late coronary angiographic restenosis after elective coronary stenting.
Methods Pre-procedural plasma levels of CRP and IL-6 were measured in 216 patients with stable angina pectoris undergoing elective coronary stenting who were included in the MedStent and DISTINCT trials. Angiographic follow-up was performed in all patients at 6 months. Angiographic restenosis was defined as diameter stenosis >50% by QCA at 6 months.
Results Baseline CRP levels were 6.45±0.78 mg/L versus 5.24±1.16 mg/L in the patent and restenosis groups, respectively (p=0.64). IL-6 levels were 0.46±0.03 ng/L versus 0.40±0.07 ng/L in the patent and restenosis groups, respectively (p=0.50). CRP levels were obtained again at the time of angiographic follow-up and were found to be similar in both groups (2.89±0.29 mg/L versus 2.61±0.63 mg/L, p=0.72). Moreover, in a sub-group of 43 patients, serial blood samples were obtained at several time points after the procedure up to 6 months. Both CRP and IL-6 plasma levels were increased significantly in response to the procedure. CRP levels peaked at 3 days (11.27±1.53 mg/L versus 4.26±0.72 mg/L at baseline, p<0.001). IL-6 levels reached maximum values after 24 hours (1.08±0.14 ng/L versus 0.53±0.08 ng/L at baseline, p<0.001). However, in this subgroup of patients, neither peak CRP nor IL-6 levels were found to predict late angiographic restenosis.
Conclusion Coronary stenting is associated with transient increases in both CRP and IL-6 levels. However, pre-procedural CRP and IL-6 levels do not predict late coronary angiographic restenosis.

1121-49 Homocysteine Levels and Methylenetetrahydrofolate Reductase Polymorphisms Are Not Associated With Restenosis After Coronary Artery Stenting

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Background: Elevated levels of plasma homocysteine have been associated with atherothrombotic diseases.Two polymorphisms, 677C/T and 1298A/C, of methylenetetrahydrofolate reductase (MTHFR) interfere with enzyme activity and, therefore, may influence homocysteine levels. We examined the possibility that elevated homocysteine and the polymorphisms of MTHFR are associated with restenosis and adverse clinical outcomes after stenting in coronary arteries.
Methods: The study population consisted of 800 patients with symptomatic coronary artery disease who were treated with stent implantation. Angiographic restenosis (50% or greater diameter stenosis at 6-month follow-up) and clinical restenosis (need for target vessel revascularization during the first year after stenting) were evaluated.
Results: Six-month follow-up angiography was done in 601 patients (75.1%). The rates of angiographic or clinical restenosis were not significantly different between patients with low or high homocysteine levels or among the genotypes of the MTHFR polymorphisms (Table). Late lumen loss and loss index were not associated with homocysteine levels or the MTHFR genotypes (Table). The one-year incidence of death or MI was not dependent on homocysteine concentrations or the genotypes (Table).
Conclusions: Our results suggest that elevated homocysteine levels or the MTHFR polymorphisms 677C/T and 1298A/C are not associated with restenosis and adverse clinical outcomes after stenting in coronary arteries.

Angiographic and clinical outcomes after coronary stenting according to MTHFR polymorphisms

	677CC	677CT	677TT	P value	1298AA	1298AC	1298CC	P value
Angiographic restenosis rate (%)	26.0	23.5	26.9	0.75	24.4	25.9	24.0	0.90
Clinical restenosis rate (%)	19.5	17.1	23.3	0.37	17.6	18.6	24.7	0.27
Late lumen loss (mm)	1.01	1.04	1.05	0.79	1.02	1.05	0.98	0.69
Loss index	0.60	0.65	0.63	0.71	0.63	0.61	0.68	0.70
Death or MI, 1y (%)	3.2	3.0	6.7	0.22	3.5	3.9	2.1	0.69

1121-50 Peroxisome Proliferator-Activated Receptor Gamma Gene Polymorphisms and Risk of Restenosis After Coronary Artery Stenting in Patients With Diabetes

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Background: Several lines of evidence suggest that activation of peroxisome proliferator-activated receptor gamma (PPARγ) may interfere with restenosis. Polymorphisms of the PPARγ gene were found to be associated with coronary artery disease and diabetes. We examined the role of the 34C/G and 1431C/T polymorphisms of the PPARγ gene in restenosis after stenting in patients with diabetes.
Methods: The study population consisted of 752 diabetic patients with symptomatic coronary artery disease who were treated with stenting. Restenosis was defined as a 50% or greater diameter stenosis six months after the intervention. Clinical outcome measures (death, myocardial infarction, restenosis-driven reintervention) were evaluated during the first year after the intervention. For analysis, patients homozygous for the common allele were compared with the carriers of the rare allele.
Results: Restenosis rates and continuous measures of restenosis (late lumen loss, loss index) were not significantly different between the PPARγ genotype groups (Table). In addition, the one-year incidences of death or myocardial infarction and reintervention were not significantly different between the groups (Table).
Conclusions: Our results suggest that the PPARγ gene polymorphisms 34C/G and 1431C/T are not associated with restenosis and adverse clinical outcomes after coronary artery stenting in diabetic patients.

Angiographic and clinical outcomes after coronary stenting according to the PPARgamma polymorphisms

	34CC	34CG + 34GG	P value	1431CC	1431CT + 1431TT	P value
Restenosis rate (%)	35.4	36.2	0.88	35.4	36.3	0.85
Late lumen loss (mm)	1.22	1.30	0.34	1.23	1.24	0.89
Loss index	0.43	0.44	0.74	0.43	0.44	0.80
Death or myocardial infarction, 1y (%)	8.3	8.6	0.89	8.0	9.7	0.46
Restenosis-driven reintervention, 1y (%)	16.6	14.9	0.60	16.8	14.5	0.47

1121-51 SU11218, a Platelet-Derived Growth Factor Receptor and Vascular Endothelial Growth Factor Receptor 2 Inhibitor Blocks Adventitial Angiogenesis and Prevents Intimal Hyperplasia After Coronary Stenting in a Porcine Model

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Background: Balloon angioplasty has been shown to produce an angiogenic response in the arterial adventitia, which is associated with restenosis in the injured segment. We hypothesized that stenting will result in a similar but more prominent adventitial angiogenic response and inhibition of this angiogenic response with a tyrosine kinase inhibitor will prevent intimal hyperplasia and restenosis after coronary stenting.
Methods: We performed coronary stenting of the left circumflex artery in 20 Yorkshire pigs. Pigs were treated with placebo or SU11218, a tyrosine kinase receptor inhibitor that blocks the activity of PDGFR and VEGFR2, which was administered subcutaneously (5 mg/kg) twice weekly for four weeks. Intravascular ultrasound was performed immediately after stenting and at four weeks for determination of lumen and intimal cross sectional areas. Adventitial microvessels were assessed ex vivo in the stented segments by microscopic computed tomography at a resolution of 16 um.
Results: The mean plasma levels for SU 11218 were 1.9-5.8ng/ml. At 4 weeks, arterial stenting resulted in a marked angiogenic response in vascular adventitia and the number of adventitial microvessels strongly correlated with the amount of instent intimal hyperpla-

sia (r=0.57, p<0.001) as well as percent area stenosis (r=0.56, p<0.001). The mean intimal cross sectional area was 2.47±1.67 in the control arteries compared to 0.52±0.52 (p<0.003) in the SU11218 treated arteries. The mean number of adventitial microvessels in the stented segment was significantly decreased in SU11218 group (16.71±3.82 versus 24.86±9.76 in the control group, p< 0.001).
Conclusions: Coronary stenting results in a prominent angiogenic response in the arterial adventitia that strongly correlates with the intimal hyperplasia and percent area stenosis. The tyrosine kinase receptor inhibitor, SU11218, markedly inhibited both the adventitial angiogenic response and in-stent hyperplastic response after stentingAngiogenic inhibitors such as SU11218 may have important therapeutic implications for preventing in-stent restenosis.

1121-52 Inhibition of In-Stent Restenosis in Porcine Coronary Arteries by Copper Chelation

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Background: In-stent restenosis is a complex process mediated by inflammatory cytokines and growth factors, which regulate inflammatory cells recruitment to the vessel wall as well as vascular smooth muscle cell migration and proliferation. Since intracellular copper metabolism plays a crucial role in the stress-induced release of FGF-1 and IL1α, both of which are important for neointima development after vessel injury, we examined the effect of tetrathiomolybdate (TTM), a clinically proven copper chelator, on in-stent restenosis in a porcine stent model.
Methods: Seventeen stents were implanted in the left anterior descending coronary artery of 17 male pigs using a stent to artery overstretch ratio of 1.2:1. Nine pigs (Gr.1) were treated daily with 10 mg/kg TTM p.o. starting 14 days prior to stent implantation and continuing until sacrifice at 28 days follow-up, whereas 8 pigs (Gr.2) served as controls. The effect of TTM on in-stent restenosis was assessed by biplane quantitative coronary angiography before and immediately after stenting as well as at 28 days follow-up. Serum ceruloplasmin activity, an indirect indicator of total copper level, was measured weekly.
Results: The two groups were comparable regarding baseline data including animal age and body weight, stent size, vessel reference diameter, and ceruloplasmin activity. Post-interventional minimal lumen diameter and overstretch ratio were similar for both groups. However, at 28 days follow-up, there was a marked difference of all parameters relevant to the in-stent restenosis in favor of the TTM-treated group: minimal lumen diameter was 2.2±0.6 mm in Gr.1 vs. 1.5±0.4 mm in Gr.2, p<0.05 and diameter stenosis was 22±18% in Gr.1 vs. 42±17% in Gr.2, p<0.05. During the entire follow-up period, ceruloplasmin activity in the TTM group was significantly decreased from 50% to 80% (p<0.0001) of its baseline level.
Conclusions: This study is the first to provide evidence that copper chelation by tetrathiomolybdate can markedly prevent in-stent restenosis. Our data also suggest that this simple and inexpensive approach is a potential tool in the management of vascular restenosis after percutaneous interventions in clinical settings.

1121-53 Long-Term Clinical Follow-Up After Diffuse In-Stent Restenosis

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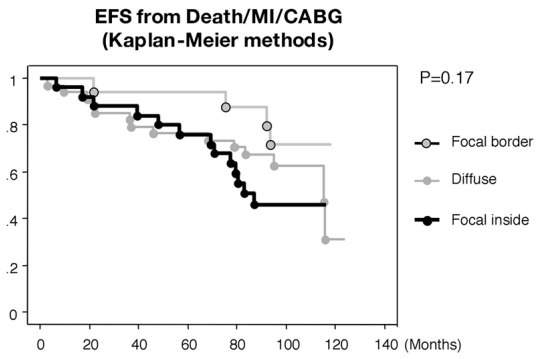
Background: Although diffuse in-stent restenosis (ISR) has been known to be refractory to repeated percutaneous coronary intervention (PCI), long-term outcome of those patients has not yet been established. Methods: To evaluate long-term (7-11yrs) clinical outcome after ISR, follow-up (FU) information was analyzed in 78 patients (pts) or 78 lesions with Palmaz-Schatz stent ISR at 6-month FU quantitative angiography. According to the angiographic appearance, ISR occurred diffusely (lesion length>10mm) in 34 pts(44%), focally inside the stent in 26 pts(33%) and focally at the stent border in 18 pts(23%). Repeat PCI was performed in 58 pts(74%). Recurrent restenosis in the diffuse type (85%) were significantly higher than those in the focally intra-stent type (12%) and in the border type (19%)(P=0.0001). Mean FU interval was 8.1+1.0 yrs among 57 surviving pts. FU rate was 98% at 8 yrs. Results: Event-free survival (EFS) rates at 8 yrs were as follows: cardiac death 92%, death 80%, death/myocardial infarction (MI)/coronary artery bypass surgery (CABG) 67%, death/MI/CABG/target lesion PCI 14%, death/MI/CABG/any PCI 6%. EFS rates (Death/MI/CABG) at 8 yrs in the diffuse type (68%) were similar with in the focally intra-stent type (51%) and focally at the stent border type (88%)(P=0.17). Conclusion: Although PCI for diffuse ISR was associated with very high recurrent restenosis rates rather than the other types of ISR, long-term clinical outcome at 7-11 yrs of FU were similar among the three groups.



1121-54 Implications of the "Watermelon Seeding" Phenomenon During Coronary Interventions for In-Stent Restenosis Insights From the Restenosis Intrastent Balloon Angioplasty Versus Elective Stenting (RIBS) Randomized Trial

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Background: The occurrence of balloon slippage ("watermelon seeding") (WMS) during treatment of patients with in-stent restenosis (ISR) has been described, but predisposing factors and the potential implications of this phenomenon remain unknown. ***Methods:*** In the *R*estenosis *I*ntra-stent: *B*alloon angioplasty vs elective *S*tenting (RIBS) randomized study, 450 patients with ISR were included. Of these, 42 patients (9%) presented WMS during the procedure. ***Results:*** WMS was detected in 26 patients (12%) in the balloon arm and 16 (7%) in the stent arm (p= 0.11). In the stent arm, WMS was only noticed during balloon predilation, never during stent implantation. As compared with 408 patients without WMS, patients with WMS tended to have more severe [% diameter stenosis (79±13% vs 76±12%, p=0.08), TIMI flow 0-1 (21% vs 8%, p=0.01)] and diffuse (length ≥15 mm: 48% vs 34%, p=0.08) ISR lesions. Patients with WMS required more balloon inflations (5.7±2.2 vs 3.5±1.9, p<0.001), longer total inflation time (184±116 vs 150±106 seconds, p=0.04), and had more frequently cross-over to stenting or ended the procedure with residual dissections (26% vs 14.5%, p=0.04) and eventually obtained poorer acute results (minimal lumen diameter 2.35±0.5 vs 2.53±0.5 mm, p=0.03). In addition, at 6-month follow-up patients with WMS had a smaller minimal lumen diameter (1.26±0.7 vs 1.61±0.7mm, p= 0.007) and a higher restenosis rate (56% vs 37%, p=0.017). On logistic regression analysis the WMS phenomenon emerged as an independent predictor of recurrent restenosis (Adjusted RR 2.1, 95%CI 1.1-4.1, p=0.04). ***Conclusions:*** The WMS phenomenon is frequently seen during treatment of patients with ISR. Long and severe lesions appear to predispose to this technical problem that never occurs during stent deployment. In patients with ISR, WMS is associated with poorer acute and long-term angiographic results.

1121-55 The Presence of Side Branches Impacts Periprocedural Enzyme Elevation and Clinical Outcome in Patients Undergoing Brachytherapy for In-Stent Restenosis

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Background: Major side branch (diameter >1.5mm, SB) involvement within the lesion subjected for Percutaneous Coronary Intervention (PCI) is known to be a contributing factor for periprocedural cardiac enzyme elevation (CE). We aimed to assess the impact of SB on CE and 6 month outcome in-patients undergoing brachytherapy for in-stent restenosis. (ISR).
Methods: Retrospective analysis of the data of 248 consecutive patients with a single vessel ISR with SB (Gp1, n=146) and without SB (Gp2, n=102) who underwent brachytherapy using both beta and gamma emitters was conducted. The procedural complications, CE, in-hospital course and 6 month clinical outcome were compared.
Results: The baseline patient and lesion characteristics were similar among the groups. Procedural variables were similar except that stent usage was more in Gp1. Baseline Creatine Phosphokinase (CPK)-MB levels were similar, but post procedure CPK-MB levels were higher in Gp1. In hospital complications were similar between the two groups. Six months follow up revealed higher restenosis and Major Adverse Cardiac Events (MACE) in Gp1.
Conclusions: Presence of SB within the restenotic segment when treated with PCI and brachytherapy is associated with higher preocedural CE and MACE at six months. Special care should taken when treating ISR lesions with SB.